REMARKS

The applicant has carefully reviewed and considered the prior art cited in the International Preliminary Examination Report and amends the claims to clearly patentably distinguish over this art. Specifically, the applicant submits new claims 10-17 covering a method of treating a patient with a chemotherapeutic composition. No treatment method is discussed, indicated or in any way contemplated in the art cited in the International Preliminary Examination Report. Specifically, the Leteurtre et al. article refers to camptothecin-induced DNA photolesions. The broad concept of the method set forth in new claims 10-17 of treating cancer with an oligonucleotide and camptothecin drug complex and the provision of any form of delivery system for such a complex is simply not disclosed, taught or suggested in this reference.

More specifically, the Leteurtre et al. reference teaches a composition comprising complexes of GC-contained oligonucleotide fragments and camptothecin (CPT)(see, for example, page 8956 column 2). The Leteurtre et al. reference does not address the specific chemical aspects of the bonding between camptothecin and DNA: i.e., the exact chemical nature of camptothecin lactone and carboxylate interactions with DNA. It is well known from the literature that camptothecins exist in two chemical forms, the "ring-closed" lactone form and the "ring-opened" carboxylate form. Leteurtre et al. teaches the conducting of experiments in 25 mM Tris-HCl, pH 7.5, 150 mM KCl, and 0.1 mM

EDTA. Under these conditions, camptothecin readily hydrolyzes to form predominantly the carboxylate form. As pointed out in the present application at, for example, page 3 lines 3 - 7, the carboxylate form of camptothecin is not active against its molecular target topoisomerase I. Thus, the hydrolyzed product or carboxylate form as taught in Leteurtre et al. is ineffective for treating cancer.

In the Leteurtre et al. reference no mention of drug hydrolysis is made and no discussion is included concerning exactly which form of camptothecin interacts with the oligonucleotide. As such, there cannot be any teaching or suggestion that would lead one skilled in the art to the concept of providing a complex of camptothecin with oligonucleotide to conserve or stabilize the active lactone form of camptothecin for subsequent cancer treatment as claimed. Thus, it is clear that the Leteurtre et al. reference provides no basis whatsoever for the rejection of new claims 10-17.

Similarly, these claims also very clearly patentably distinguish over the Green et al. reference.

The Green et al. reference teaches the utilization of antisense oligonucleotides which are administered to the cell in amounts sufficient to inhibit expression of the antiapoptotic gene, thus rendering the cell susceptible to induction of apoptosis utilizing a chemotherapeutic agent such as camptothecin (note, for example, column 7 line 63 to column 8 line 25 of the Green et al. patent). At column 9, lines 11 - 19, the use of a pharmaceutical combination of the antisense oligonucleotide and therapeutic agent is

disclosed and mixtures of the two components are referenced. In a true chemical sense, however, a mixture is not a complex as claimed in the present invention and, accordingly, the present invention distinguishes from this reference.

Stated another way, the Green et al. reference does not teach a combined camptothecin-oligonucleotide complex where a key function of the nucleotide is to maintain the active lactone form of the camptothecin. In the pharmaceutical compositions taught by Green et al., conditions are not conducive to stabilizing the active lactone form of camptothecin. In contrast, in the present invention as set forth in claims 10-17, the active lactone form is conserved by complexing with the oligonucleotide.

Administering camptothecin and oligonucleotide independently as proposed by Green et al. will not result in this stabilization of the active lactone form. This is clearly evident when one reviews the work of the Green et al. reference wherein stock solutions of camptothecin were made up in DMSO in the absence of oligonucleotide and these solutions were then diluted into aqueous media. In Green et al. the direct complexation of camptothecin and resultant stabilization of the active lactone is not described, nor is it achieved, and it is not obvious from their described formulations that camptothecin lactone stabilization by complexing with oligonucleotide would occur. Thus, the present invention as set forth in all the claims clearly patently distinguishes over the Green et al. reference and these claims should be allowed.

As should be further noted, the Green et al. reference does not contain any description or even any remote suggestion as to how one skilled in the art would physically formulate a camptothecin-oligonucleotide complex of the type set forth and claimed in the present application. Further, the Green et al. reference does not teach or suggest that such a complex would have any unique advantage: much less that the active lactone form of camptothecin is stabilized by the formation of the complex so that subsequent effective cancer treatment may be provided. This is because the Green et al. reference does not even consider the relative merits and effectiveness of the two forms of camptothecin in treating cancer. As such, it is clear that the Green et al. reference fails to provide any teaching or suggestion to lead one skilled in the art to the present invention as claimed. This is true whether it is considered alone or in combination with the prior art discussed on pages 1, 2, 5 and 6 of the description. Therefore claims 10-17 very clearly patentably distinguish and should be formally allowed.

Similarly, new claims 18-25 to a chemotherapeutic composition also patentably distinguish over this art. These claims substantially correspond to original claims 1-8 with what was original claim 1 rewritten and presented as new claim 18. This claim has been modified slightly to more clearly identify the invention and emphasize the distinguishing features thereof that support patentability. Specifically, a chemotherapeutic composition is claimed comprising an oligonucleotide-camptothecin drug complex wherein a pharmaceutically effective amount of active lactone

camptothecin drug dissociates from the oligonucleotide within the body and exerts its therapeutic activity. Preservation of the active lactone camptothecin drug is not taught in the cited art. Thus, no chemotherapeutic composition is taught or suggested in either the Leteurtre et al. or Green et al. references and, accordingly, these claims patentably distinguish over the art and should be allowed.

Of course, claim 9 should also be allowed since the references cited in the International Search Report fail in any way to suggest a method for delivering oligonucleotide-stabilized lactone forms of camptothecin drugs to a host.

In summary, upon careful review and consideration it is believed the Examiner will agree that all the pending claims patentably distinguish over the art and should be formally allowed.

Respectfully submitted,

KING AND SCHICKLI, PLLC

Warren D. Schickli
Registration No. 31,057

247 North Broadway
Lexington, Kentucky 40507
(859) 252-0889

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Date July 19, 2001 Sandy Williams

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

THOMAS G. BURKE ET AL.

Serial No.: 09/807,332

Filing Date: April 11, 2001

For: OLIGONUCLEOTIDE DELIVERY SYSTEMS FOR CAMPTOTHECINS

VERSION WITH MARKINGS TO SHOW CHANGES MADE

10.) A method of treating a patient with a chemotherapeutic composition, comprising:

administering an oligonucleotide-camptothecin drug complex which incorporates sufficient amounts of active lactone camptothecin drug to exert therapeutic activity when administered to the body, wherein the camptothecin drug dissociates from the oligonucleotide within the body and exerts its therapeutic activities.

11.) The method claim 10, wherein the camptothecin drug is selected from a group consisting of camptothecin; 10-hydroxycamptothecin; topotecan;

9-aminocamptothecin; 9-nitrocamptothecin; 10-hydroxycamptothecin; 10,11-methylenedioxycamptothecin; 9-nitro-10,11-methylenedioxy-camptothecin; 9-chloro-10,11-methylenedioxycamptothecin; 9-amino-10,11-methylenedioxycamptothecin; 7-ethyl-10-hydroxycamptothecin (SN-38); DX-8951; GG211; 7-trimethylsilylmethylcamptothecin; and mixtures thereof.

12.) The method of claim 10, wherein the oligonucleotide is selected from the group consisting of single-stranded DNA, double-stranded DNA, antisense DNA, RNA, and catalytic RNA.

13.) The method of claim 10, wherein said camptothecin drug is noncovalently associated with the DNA and naturally dissociates in the body to release the active lactone form of the drug.

14.) The method of claim 10, wherein said camptothecin drug is covalently tethered to the oligonucleotide molecule and can be metabolically released from the oligonucleotide within the body.

15.) The method of claim 10, wherein said oligonucleotide-camptothecin drug complex is held within macromolecular assemblies of viral oligonucleotide vectors having a viral gene delivery system including retroviruses, adenoviruses, adeno-associated viruses, *Herpes* viruses, *Vaccinia* viruses, and other virus particles.

16.) The method of claim 10, wherein said oligonucleotide-camptothecin drug complex is held within macromolecular assemblies of non-viral oligonucleotide vectors having a non-viral gene delivery system including transfection vehicles, naked DNA for injection, gene gun particles, liposomes including cationic liposomes, virosomes, receptor-mediated delivery vehicles, and biodegradable and non-biodegradable polymer matrixes.

17.) The method of claim 10, further including lipid so as to form a lipid:oligonucleotide-camptothecin drug complex from a surfactant, lipid or mixture thereof, said lipid defining a compartment wherein said oligonucleotide-camptothecin drug complex exists and the camptothecin drug is held and protected from hydrolysis and is thus stabilized.

18.) A chemotherapeutic composition, comprising an oligonucleotide-camptothecin drug complex including a pharmaceutically effective amount of active lactone camptothecin drug that dissociates from the oligonucleotide within the body and exerts therapeutic activity.

19.) The chemical composition of claim 18, wherein the camptothecin drug is selected from a group consisting of camptothecin; 10-hydroxycamptothecin; topotecan; 9-aminocamptothecin; 9-nitrocamptothecin; 10-hydroxycamptothecin; 10,11-methylenedioxycamptothecin; 9-nitro-10,11-methylenedioxy-camptothecin; 9-chloro-10,11-methylenedioxycamptothecin; 9-amino-10,11-methylenedioxycamptothecin; 7-ethyl-10-hydroxycamptothecin

(SN-38); DX-8951; GG211; 7-trimethylsilylmethylcamptothecin; and mixtures thereof.

20.) The composition of claim 18 wherein the oligonucleotide is selected from the group consisting of single-stranded DNA, double-stranded DNA, antisense DNA, RNA, and catalytic RNA.

21.) The composition of claim 18 wherein said camptothecin drug is noncovalently associated with the DNA and naturally dissociates in the body to release the active lactone form of the drug.

22.) The composition of claim 18 wherein said camptothecin drug is covalently tethered to the oligonucleotide molecule and can be metabolically released from the oligonucleotide within the body.

23.) The composition of claim 18 wherein said oligonucleotide-camptothecin drug complex is held within macromolecular assemblies of viral oligonucleotide vectors having a viral gene delivery system including retroviruses, adenoviruses, adeno-associated viruses, *Herpes* viruses, *Vaccinia* viruses, and other virus particles.

24.) The composition of claim 18, wherein said oligonucleotide-camptothecin drug complex is held within macromolecular assemblies of non-viral oligonucleotide vectors having a non-viral gene delivery system including

transfection vehicles, naked DNA for injection, gene gun particles, liposomes including cationic liposomes, virosomes, receptor-mediated delivery vehicles, and biodegradable and non-biodegradable polymer matrixes.

25.) The composition of claim 18 further including lipid so as to form a lipid:oligonucleotide-camptothecin drug complex from a surfactant, lipid or mixture thereof, said lipid defining a compartment wherein said oligonucleotide-camptothecin drug complex exists and the camptothecin drug is held and protected from hydrolysis and is thus stabilized.